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Pennie & Edmonds
1667 K Street NW
Washington, DC 20006

EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,491	KUSK, PHILIP	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *5-9,11-13 and 16-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/14/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, claims 1-15, with respect to the bone sialoprotein gene, polymorphisms A1496G in the paper received 9/22/03 is acknowledged. The traversal is on the grounds that (1) there was no objection to lack of unity in the international phase of this application; (2) All of the proteins coded by the genes in claim 1 have special "reference to bone," while TGF-β correlates to a number of non-bone and non-calcification related disorders and (3) there would be no burden to examine the pending claims. Applicant also submits that an election of species should not be required as to individual polymorphisms within a single specific gene promoter since a search of all such species would pose little difficulty . These are not found persuasive because:

(1) The US examining authority is not bound by the findings of the international authority, with regard to lack of unity or with regard to other aspects of search and examination. In the instant case, a reasoning which supports the finding of lack of unity has been set forth.

(2) This is not persuasive because the "special reference to bone" is not clearly defined in the specification or the claims. Osteopontin, while being a principle glycoprotein of bone, is also expressed in other tissues including dentine, urinary stones, and the kidney (OMIM entry 166490). Thus, even the genes within applicant's recited invention are not exclusive to bone tissue. Applicant further sets forth in a foot note that the teachings of Grainger *et al.* are do not provide an enabling disclosure, much less applicant's invention. First, with regard to the lack of enablement of Grainger *et al.*'s methods, applicant's arguments are not supported by evidence, and attorney's arguments are not substitute for evidence on the record. Further, it is noted that

the Grainger *et al.* method claims eventually matured into a US Patent (US 5998137) supported by disclosure identical to that in the cited WO document, which is presumed to valid and thus enabled.

Applicant states on more than one occasion that Grainger *et al.* do not teach applicant's invention. The examiner does not set forth that Grainger *et al.* teaches applicant's invention, merely that the feature that joins applicant's multiple inventions is not a special technical feature in view of the prior art. As further support of this assertion, Ye *et al.* (Journal of Biological Chemistry, Vol. 271, p. 13055-13060) teach a promoter in the human stromelysin-1 promoter which is associated with coronary atherosclerosis (abstract and throughout). Thus, in view of these, it is maintained that there is no special technical feature that joins the claimed inventions, and the lack of unity as set forth is maintained.

(3) This is not found persuasive because under the PCT rules, a showing of lack of unity is required for proper restriction of claims and such a showing has been made. Furthermore, however, it would indeed pose a serious burden on the examiner to examine claims all together as they would require the search and examination of polymorphisms and associations of at least four different distinct genes. Although the international search report is a beginning point for the search in the US case, the examiner is bound to perform a separate and thorough search of all claimed subject matter, including herein methods of assessing predispositions using polymorphisms within four different genes, products, and methods of therapy.

MPEP 801 states,

> "This chapter is limited to a discussion of the subject of restriction and double patenting under Title 35 of the United States Code and Title 37 of the Code of Federal Regulations as it relates to national applications filed under 35 U.S.C. 111(a). **The discussion of unity of invention under the Patent Cooperation Treaty Articles and Rules as it is**

applied as an International Searching Authority, International Preliminary Examining Authority, and in applications entering the National Stage under 35 U.S.C. 371 as a Designated or Elected Office in the U.S. Patent and Trademark Office is covered in Chapter 1800 (emphasis added)."

Referring to Chapter 1800, MPEP 1893.03(d) states,

"The principles of unity of invention are used to determine the types of claimed subject matter and the combinations of claims to different categories of invention that are permitted to be included in a single international or national stage patent application. The basic principle is that an application should relate to only one invention or, if there is more than one invention, that applicant would have a right to include in a single application only those inventions which are so linked as to form a single general inventive concept. A group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature. The expression special technical features is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes **over the prior art** (emphasis added)."

MPEP 1800 does not set forth the level of search burden as a standard for proper division of claims under lack of unity practice.

The requirement is still deemed proper and is therefore made FINAL.

2. Upon reconsideration, the two polymorphisms within the sialoprotein gene will both be considered.

3. In view of applicant's election of the bone sailoprotein gene, polymorphism BSP-A1496G, and the rejoinder of BSP-G1869A by the examiner, claims 1, 2, 3, 4, 10, 14, and 15 are under consideration herein. Claims 5-9 and 11-13 and 16-24 are withdrawn from prosecution because these contain non-elected genes and combinations of polymorphisms and/or non-elected inventions.

4. The preliminary amendments to the specification and claims filed on 18 July 2001 and 5 February 2002 have been entered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 3, 4, 10, 14, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is not clear how the single recited method step accomplishes the goal set forth in the preamble of the claim. The preamble of the claim recites "A method of assessing an individual's predisposition to a selected calcification condition status," yet the single positive process step of the recited method only requires determining the genotype of the promoter of the bone sialoprotein gene (elected embodiment). The method step of the claim does not set forth how the genotyping is related to assessing a predisposition, and thus, it is not clear if applicant intends to be claiming a method of genotyping or a method of assessing a predisposition, as there is no nexus between the recited goal and the required process. The remaining rejected claims depend from claim 1 and are indefinite over this same recitation.

Claim 1 is further indefinite over the recitation "the bone sialoprotein gene" because this phrase lacks proper antecedent basis in the claims. The claim is indefinite over this recitation because there are at least two bone sialoprotein genes known in the prior art (BSP I and BSP II) and it is not clear from the recitation of the claims which one applicant intends to be referring to as "the bone sialoprotein gene." For example, Fisher *et al.* teach the human bone sialoprotein, referred to as the BSP, was formerly called the BSP II to distinguish it from BSP I until BSP I was renamed osteopontin. The current OMIM entry 166490, however, teaches that bone

sialoprotein is an alternative title for osteopontin, and OMIM entry 147563 refers to a bone sialoprotein II, which cites the Kim *et al.* reference cited in this specification as teaching a sequence of "the bone sialoprotein gene." Thus, there is a lack of clarity in the prior art as to the meaning of "the bone sialoprotein." Therefore, clarification of the claims is required to provide proper antecedent basis for the phrase "the bone sialoprotein." The remaining rejected claims depend from claim 1 and are indefinite over this same recitation. Furthermore, claims 3, 4, and 10 are also indefinite because they separately refer to "the bone sialoprotein gene."

Claim 2 is indefinite over the recitations of "high" and "low" peak bone mass or rate of bone loss because "high" and "low" are relative terms and no standard for determining what is "high" or "low" is given in the claims or the specification.

Claim 4 is indefinite over the recitation "BSP-A1496G (SEQ ID NO: 13)" the recitation "BSP-G1869A (SEQ ID NO: 14)." The claim is indefinite over this recitation because, first, the allelic identifier are arbitrary identifiers whose definition is not clear from the specification as the numbering system referred to in the specification is not a fixed numbering system. The specification teaches that "A DNA sequence" of the human bone sialoprotein promoter has been published and submitted to GenBank L24756 (p. 6 of spec), and that the locations are numbered from the start of the "published sequence (p. 7 of spec)." However, reliance upon a GenBank record does not provide adequate clarity for the claimed invention, as the content and numbering in a GenBank record can change over time as the records can be updated as time passes. In this case a potential update to the cited GenBank record wherein a revision includes the addition or deletion of a single nucleotide would result in a complete change in the numbering system. In these claims, this reliance of an external GenBank sequence for a numbering scheme is similar to

the recitation of a trademark, in that the GenBank accession number does not represent a fixed disclosure of a sequence, but instead refers to a record that is constantly able to be updated and modified. Applicant should amend the specification to include the sequences which are referred to by GenBank accession numbers (and comply with the remainder of the sequence rules) and file a 132 declaration with evidence showing and stating that the newly filed sequence is identical to the sequence that was in GenBank at the time the invention was filed. From the specification it is clear that BSP-A1496G refers to a polymorphism at position 1496 of the "published sequence" wherein this position can have an "A" or a "G," and similarly, BSP-G1896A refers to a polymorphism at position 1896 of the published sequence, wherein this position can have a "G" or an "A." However, it is further not clear from the claims or the specification what is intended by the inclusion of the sequence identifiers in the parentheses after the recitation of the polymorphism identifiers. Both of these SEQ ID NO's refer to 31 base pair sequences which overlap with the published GenBank L24756 record at the position of the respective polymorphisms. The SEQ ID NO's of the specification recite the same nucleotide at the variable position as the wild type. It is not clear, therefore, if applicant is trying to limit claim 4 to the detection of the particular variant (that is an A at position 1496, for example) or if the recitation of the sequence identifiers has some other intention in the claims.

Claim 10 is indefinite over the recitation "lower peak bone mass" because it is unclear what the peak bone mass would be "lower" than; there is no standard for comparison given for this relative term. Claim 10 is further indefinite over the recitation "at position 1496 bp" and the recitation "1869 bp" because, like noted in claim 3, these recitations depend on the GenBank sequence numbering which is not a fixed numbering system.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 3, 14, and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to methods for assessing an individual's predisposition to a selected calcification condition status, which method comprises determining the genotype of the promoter of the bone sialoprotein gene. Claim 2 limits claim 1 such that the calcification condition status is having high or low peak bone mass or having high or low rate of bone loss. Claim 3 requires that it is determined whether the individual is homozygous or heterozygous for an allelic variation of the bone sialoprotein gene. Claims 14 and 15 further describe the methodology used to genotype the bone sialoprotein gene.

Thus, the rejected claims encompass the use of any polymorphism within the promoter of any bone sialoprotein gene from any organism. The specification teaches two such polymorphisms from with in the gene disclosed by Kim *et al.* as the human sialoprotein gene promoter, represented in GenBank accession L24756. The polymorphisms are at positions 1496 and 1869 of the published sequence. The specification does not provide any other description of allelic variants or polymorphisms within this genus. Furthermore, while the instant claims require sequencing "the promoter" of "the sialoprotein gene," the claims do not further define

either of these particular sequences. Thus, broadly interpreted, "the promoter" of the sialoprotein gene could encompass sequence multiple thousands of base pairs upstream of the transcription initiation site of this gene. Furthermore, the specification does not set forth with clarity which gene is "the sialoprotein gene (as discussed in the 112 2nd paragraph rejection) and thus promoters other than those described in the cited GenBank Accession number which are not described and for whom no polymorphisms are disclosed are encompassed within the recitation of these claims.

As noted, this large genus is represented in the specification by the disclosure of two single nucleotide polymorphisms within the human sialoprotein gene promoter taught in GenBank L24756. Thus, applicant has express possession of only two species in a genus which comprises many, many different possibilities.

In the application at the time of filing, there is no record or description which would demonstrate possession of any additional polymorphisms within the "published" human sialoprotein promoter sequence, or within portions of the promoter sequence that may be upstream of the published sequence, or within the sialoprotein sequence from other organisms, let alone any additional polymorphisms within these sequences that are useful for assessing an individual's predisposition to a selected calcification condition status.

8. Claims 1, 2, 3, 4, 10, 14, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method which determines that an individual having a "G" at the BSP-A1496G polymorphism and/or an "A" the BSP-G1869A polymorphism is more likely to have increased bone mass compared to individuals who have an "A" at the BSP-A1496G polymorphism or a "G" at the BSP-G1869A polymorphism of the bone

sialoprotein gene, does not reasonably provide enablement for methods which assess an individual's predisposition to the broadly recited "calcification condition status" or methods which utilize other polymorphisms within the bone sialoprotein gene promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the Invention

The invention is concerned with providing a method for assessing an individual's predisposition to a calcification condition status via the genotyping of the promoter of the bone sialoprotein gene. Thus, the practice of the method relies on the showing of an association between a particular genotype and a particular calcification condition status.

The rejected claims are drawn to methods for assessing an individual's predisposition to a selected calcification condition status, which method comprises determining the genotype of the promoter of the bone sialoprotein gene. Claim 2 limits claim 1 such that the calcification condition status is having high or low peak bone mass or having high or low rate of bone loss. Claim 3 requires that it is determined whether the individual is homozygous or heterozygous for an allelic variation of the bone sialoprotein gene. Claim 4 recites that the allelic variation of the bone sialoprotein gene promoter is BSP-A1496G or BSP-G1869A. Claim 10 depends from claim 3 and recites that at least on copy of the bone sialoprotein has an adenine or a guanine at position 1496 or position 1869 wherein the adenine at position 1496 and guanine at position 1869 are associated with lower peak bone mass. Claims 14 and 15 further describe the methodology used to genotype the bone sialoprotein gene.

It is noted that in this rejection the use of the terms BSP-A1496G and BSP-G1869A refer to polymorphisms that were disclosed in the instant specification as being within the published sequence GenBank L24756, the human bone sialoprotein gene, as the gene was published in version GI: 438617 of the GenBank record, said record being dated 29 September 1994. While the examiner has noted the use of this numbering system is problematic (see 112 2nd paragraph rejections herein), this system is used in this rejection and throughout the office action due to lack of a clearer system, as no alternative system is provided in the specification or the prior art for referring to these novel polymorphisms.

Breadth of the claims

Thus, the rejected claims encompass determining a predisposition to any "calcification condition status" which could include a wide variety of diseases, disorders, and phenotypes including, for example, osteoporosis, atherosclerosis, bone mineral density, rate of bone loss, placenta calcification, renal calcification, calcification of tendons or cartilage, etc. Claim 2 is limited so that the recited calcification condition status is having a high or low peak bone mass or rate of bone loss.

Additionally, the claims encompass the use of any genotype or polymorphism within any sialoprotein gene promoter region, including portions of the promoter that are upstream of that disclosed in the Kim *et al.* reference and GenBank accession number, which the specification sets forth as "A sialoprotein gene promoter sequence."

Teachings in the Specification and Working Examples

The specification provides two novel polymorphisms within the 5' untranslated region of a gene taught by Kim *et al.* and referred to as the human bone sialoprotein promoter sequence,

see GenBank L24756. Within this sequence, applicant identified polymorphisms at positions 1496 (A→G) and 1869 (G→A) wherein the first version is the version present in the published sequence and the second allele is the alternate allele identified by applicant (p. 7, lines 21-30). The specification refers to these variations as BSP-A1496G and BSP-G1869A, respectively.

In example 1 of the specification (beginning on page 22), applicant teaches the screening of the DAN from 133 women for the polymorphisms, via amplification of fragments of DNA and restriction digestion. For the BSP-A1496G polymorphism, SEQ ID NO: 1 and SEQ ID NO: 2 were used as amplification primers, and for the BSP-G1869A polymorphism, SEQ ID NO: 3 and SEQ ID NO: 4 were used as amplification primers (p. 23-24). The specification teaches that for the BSP-A1496G polymorphism, the "A" allele was most abundant, and for the BSP-G1869A, the "A" allele was also more abundant (p. 29). Further, the example demonstrates that there is a significant association between these polymorphisms and bone mass as represented by bone mineral content and bone mineral density measurements (p. 31). Specifically, patients with the "A" allele at 1469 and/or the "G" allele at 1869 are more likely to have higher bone mass than patients with the opposite alleles (p. 31-32). Further, and with regard to claim 2 in particular, the specification specifically states that the polymorphisms did not appear to have a statistically significant impact on the change in bone mass over time (see p. 32), and that the observations presented strongly indicate that the BSP polymorphisms influence peak bone mass rather than the rate of bone loss (p. 32, lines 18-20).

The specification is silent as to additional polymorphisms within the bone sialoprotein gene as disclosed by Kim *et al.* or as to polymorphisms within any bone sialoprotein gene of other organisms or promoter sequence of the gene that is upstream of the disclosure of Kim *et al.*

The specification does not provide any evidence or disclosure that these polymorphisms are associated with any additional phenotypes related to calcification status, or any showing that these two disclosed polymorphisms are related to all indicators of calcification status or all disease which are related to calcification status. While low bone mass is an indicator of osteoporosis accepted in the prior art, the specification does not provide any guidance as to whether any of the bone masses observed in the instant study were sufficiently low so as to be indicators of such a disease or a predisposition to such a disease as no data is given as to the bone mass of the patients at particular ages or compared to other patients.

State of the prior art and Level of unpredictability

The prior art is silent as to polymorphisms within any bone sialoprotein gene promoter.

However, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. First, it is unpredictable which portions of a particular nucleic acid sequence will be polymorphic, and absent rote screening methods of possible sequences, there is no way to predict which sequences will be polymorphic. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-

globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed two polymorphisms in the promoter of a human bone sialoprotein gene, it remains highly as to what other polymorphisms may or may not be present in this promoter, and with which additional phenotypes the disclosed and putative unknown polymorphisms may be associated. Thus, the claimed method directed towards the assessment of a predisposition to a selected calcification condition status requires the knowledge of unpredictable and potentially non-existent associations between the instantly disclosed polymorphisms and additional calcification condition statuses, and between undisclosed polymorphisms and such statuses.

Quantity of Experimentation

The practice of the claimed invention commensurate in scope with the instant claims would require a high degree of experimentation to identify additional polymorphisms and to associate these polymorphisms with any or all calcification condition statuses. Likewise, even with respect to the disclosed polymorphisms within the bone sialoprotein gene, the practice of the claimed invention would require extensive further work to determine which calcification conditions can be predicted using even these polymorphisms. That this work would be unpredictable is exemplified in the specification which demonstrates that while the two disclosed polymorphisms may be predictors of bone mass within the tested population, they are not predictors of the rate of bone loss.

Conclusion

Thus, having considered each of these factors, namely the breadth of the claims, the high level of unpredictability in the related art, the lack of guidance in the specification and the prior art, and the high quantity of experimentation, it is concluded that it would require undue experimentation to practice the claimed invention commensurate in scope with the instant claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 2, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim *et al.* (Matrix Biology, Vol. 14/1994, p. 31-40).

Kim *et al.* teach a method which comprises determining the genotype of the promoter of the bone sialoprotein gene. Specifically, Kim *et al.* sequence the promoter of the bone sialoprotien gene (p. 33, first column, and Figure 4). Furthermore, Kim *et al.* teach a method which genotypes the promoter of the bone sialoprotein gene which comprises amplifying a relevant portion of the DNA of said gene promoter (p. 33-34). This reference is considered to anticipate the method recited in claims 1, 2, and 14 because it meets the single process step recited in the claims. As the claim is currently drawn, the recited preamble does result in a manipulative difference between the method of the claimed invention and the method of the prior art, and thus, the method taught by Kim *et al.*, which inherently determines the nucleotide present at each position in the sequence of the promoter of a bone sialoprotein gene (thus genotyping the promoter), meets the limitations of the claimed invention. The recitation of claim 2 further modifies the preamble of the claim.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM. Please note that on January 13, 2003 the examiner's telephone number will change to (571) 272-0753.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (703) 308-1119. Beginning January 13, 2003 Gary Benzion's telephone number will be (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196. Beginning January 13, 2003 the receptionist's telephone number will be (571)272-0507.

Juliet C Switzer
Examiner
Art Unit 1634

December 24, 2003